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REPLY BRIEF	Attorney Docket No.	TOPI-002CIP
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Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1611
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	Title: *Methods and compositions for treating headache pain with topical NSAID compositions*	

Sir:

This Reply Brief is filed in response to the Examiner's Answer mailed by the Office on July 10, 2009.

Please charge any required fees to Deposit Account No. 50-0815, reference no. TOPI-002CIP.

REPLY BRIEF

In this Reply Brief, the Appellants address several issues raised in the Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

In this Reply Brief, the Appellants address specific assertions made by the Examiner in responding to Appellants' arguments. However, before addressing these specific assertions of the Examiner, the Applicants wish to clarify the specific nature of the target headaches to which the claims are directed, as the Examiner's position appears to be based on a misconception of the nature of the target headaches specified in the claims.

An element of all of the claims at issue is to ameliorate headache pain "caused by a tension headache, migraine headache, indomethacin responsive headache or cluster headache". As has been stated in prior arguments, these headaches are all *central* headaches, caused by *disturbances in the central nervous system* (i.e., deep in the brain). Thus, the underlying site of pathophysiologic mechanism of these specific headaches is within the skull and within the brain and therefore not penetrated or reached by the topical NSAID formulations described within the application.

In the Examiner's answer, it is clear that the Examiner continues to operate under the erroneous assumption that all pain conditions and headache pain conditions are the same, with the same underlying pathophysiolgy such that all pain conditions and headache pain conditions can be treated in the same manner. The Examiner continues to ignore the distinction between pains caused by *localized* musculoskeletal mechanisms (e.g., arthritic joints, muscle spasms, etc.), versus *central* headaches such as migraine, cluster, tension headaches, and indomethacin responsive headaches (IRH), as in the current claims.

Because the target headaches of the present claims are caused by disturbances in the central nervous system (i.e., deep in the brain), the claims are directed to methods in which the NSAID is applied to a site that is distal from the site

of pain/headache generation. The approach of the claimed invention is therefore in contrast to the NSAID references cited by the Examiner where the NSAIDs that are systemically administered to reach the site of pain (Pradalier and Cluff) and where the site of pain is proximal to the site of application (i.e., Toppo).

In addition, the mechanisms of action of an NSAID agent is vastly different then a local anesthetic as is described by Caldwell and Galer. Caldwell utilizes topical application of a local anesthetic drug to cause a nerve block in a peripheral nerve by placing the topical local anesthetic formulation in a very precise location to penetrate the skin and reach particular nerves in the head. The current application and claims describe only the use of anti-inflammatory drugs placed on the keratinized surface of the head without specific placement to interact with these nerves and without a resultant reduction in these nerves' activity (i.e., no nerve block is produced).

I. Claims 1-18 and 24-33 are patentable under 35 U.S.C. §103(a) over the combined teachings of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo.

Group I: Claims 1-18, 24-26, 28, and 32-33

As fully developed in the Appeal Brief, the claims of this group are directed to methods for treating specific types of headache pain. The specific types of headache pain are caused by a migraine headache, indomethacin responsive headache syndrome (IRH), tension headache, or cluster headache. The claims specify of topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in the topical formulation to a keratinized skin surface of the head of the host.

As such, the claims are directed to a method in which a topical NSAID is applied to a topical location that is distal from the origin of pain, i.e., the central brain.

In maintaining the rejection in the Examiner's answer, it is believed that the Examiner has:

A) made incorrect assertions with respect to the fact that not all elements of the claim are taught or suggested in the cited combination of references;

B) incorrectly discounted the evidence of lack of expectation of success; and

C) not provided a valid reason to combine the references.

Each of these errors is developed more fully below.

A) The combination of the references fails to teach or suggest each and every element of the claims.

As developed in the Appellants' brief, the combination of references put forth by the Office actually fails to teach or suggest all of the elements of the claimed invention.

Specifically, the target headaches recited in the claims are tension headaches, migraine headaches, IRH syndromes or cluster headaches. By definition, these target headaches are centrally-mediated headaches. Furthermore, the site of application of the topical formulations is not the brain, but rather a keratinized skin surface of the head outside of the skull. As such, the site of application is not at the site of pain generation, but distal from the site of pain. Accordingly, an element of the claims is topically applying the NSAID at a site distal from the site of pain.

In maintaining the rejection in the Examiner's answer, the Examiner has alleged that the features upon which the Appellant relies are not recited in the rejected claims. Specifically, the Examiner has alleged that the above claim element of topically applying an NSAID distal from the site of pain is not present in the claims.

However, as explained above, this particular element is indeed present in the claims because the claims recite:

(a) treating either a tension headache, migraine headache, IRH syndrome or cluster headache (which by definition are centrally-mediated headaches); and

(b) applying a topical NSAID at a keratinized skin surface of the head, which is not the site of the painful condition (i.e., deep in the brain).

In view of this interpretation, the cited references clearly fail to teach or suggest the above claim element.

Pradalier and Cluff disclose treatment of migraine with clinically significant systemic blood levels of NSAID, and not topical NSAIDs as in the current claims. Toppo discloses a method of topical administration of NSAIDs for treatment of arthritis, where treatment is applied "directly to afflicted areas of the body", e.g., at the site of inflammation and pain generation. This teaching is therefore in contrast to the current claims, in which the site of application of the NSAID (e.g., the forehead) is not the site of pain or the "afflicted area" (i.e. deep in the brain) but distal to this site.

The Examiner further cites Caldwell for teaching the treatment of migraine "by topical delivery of pain relief composition to keratinized skin proximal to the nerves associated with migraine headache" (Examiner's Answer, p. 8). However, Caldwell discloses an *entirely different* drug with an entirely different mode of activity within the body (nerve blocking agent). One of ordinary skill in the art would not extrapolate using the locally-applied nerve blocking agent in Caldwell to the teaching of the other references to topically apply an NSAID for treatment of central headaches as in the current claims. In addition, Caldwell teaches the exact placement of the nerve blocking agent on the head because this nerve blocking drug will only relieve headache pain if it directly interacts with specific nerves in the head and thereby produces a nerve block. In contradistinction, the current claims utilize an antinflammatory drug placed on the keratinized skin of the head that reduces inflammation and does not work by producing a nerve block.

The Examiner is therefore combining references which teach the systemic administration of NSAIDs for migraine, with a method of topical administration of NSAIDs where treatment is applied "directly to afflicted areas of the body", e.g., the site of inflammation and pain generation. However, systemic administration results in NSAID being delivered directly to the site of pain, i.e. the brain. Similarly, Toppo is teaching administration of an NSAID directly to the site of pain generation, i.e. the brain. Caldwell does not even teach an NSAID, but a completely different type of active agent, with a specific site of application so as to directly interact with specific nerves so as to produce a nerve block.

The Appellants therefore maintain that the above references, either alone or in combination, do not contain the element of using a topical NSAID which is applied to a site which is not the site of pain (i.e., the brain in central headaches) and does not result in a nerve block.

Accordingly, the combination of references fails to teach or suggest the element of using a topical NSAID for treatment of headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache (i.e., a central headache), as claimed.

B) The cited references fail to provide one of ordinary skill in the art with predicted success in the claimed invention.

As discussed in the Appeal Brief, the claimed invention is based on the inventor's discovery that one could in fact treat the pain of *central* headaches (such as migraine, indomethacin responsive, tension and cluster headaches) by applying a *topical* NSAID formulation to a keratinized skin surface of the head. This discovery is sharp contrast to the contrary to the accepted belief of those of ordinary skill in the art at the time the application was filed, which held that the target headaches had to be treated with systemic NSAID delivery.

The Appellants maintain that their discovery was unexpected and have provided extensive evidence in the record to support their position, where this evidence demonstrates that::

(1) it was believed that the underlying pathophysiologic mechanism of migraines, indomethacin-responsive headaches, tension headaches, and cluster headaches were related to abnormalities deep within the brain;

(2) it was known that topical formulations act locally and do not produce any significant drug levels in the systemic circulation nor in the brain; and

(3) it was believed that oral NSAIDs would only successfully treat headache symptoms if clinically significant systemic blood levels were achieved. See e.g., the declaration of record provided by Dr. Newman.

(4) though topical NSAIDs have been available to physicians and headache experts for decades, there is no mention anywhere in the medical literature of the use of topical NSAIDs as described in this application for the treatment of headache; thus Drs. Galer and Newman, both of whom are headache specialists, were surprised at their unexpected findings and therefore filed this patent application.

In attempting to discredit the evidence provided by the Appellants, the Examiner has alleged that "even if the pathophysiologic mechanism of migraine is deep in the brain, it was taught to be treated by topical application of pain relief agents to the forehead and occipital areas as taught by Caldwell" (Examiner's Answer, p. 16).

However, as described above, Caldwell is concerned with an entirely different type of active agent which works by an entirely different mechanism. Specifically, the local anesthetics which are disclosed in Caldwell act directly interacting with specific nerves within the head and thereby causing a blocking of these nerves' conduction. In contrast, NSAIDs do not block nerve conduction and this patent application does not describe the site of application has to be at these specific sites to interact with these particular nerves. Therefore, Caldwell does not discredit the evidence of the unexpected nature of the invention which is part of the record.

In maintaining this rejection, the Examiner continues to discount the evidence provided by Dr. Newman, a noted expert in the fields of headache and pain

management. In this Declaration, Dr. Newman states the fact of record that oral NSAIDs were known to successfully treat headache symptoms only if *clinically significant systemic blood levels were achieved.* As such, evidence is present in the record that one of ordinary skill in the art at the time of the invention would not expect topical NSAIDs to be successful in treating *central* headaches. One would not expect success because it was known that topical formulations act locally and do not produce significant systemic drug levels, which were believed to be required for NSAID efficacy in treating the claimed target headaches.

Furthermore, the Examiner has not provided any evidence to rebut the extensive evidence provided by the Appellants that one of ordinary skill in the art at the time of the invention would not have expected a *topical* NSAID to work in treating a headache of *central* origin. The Examiner has merely cited Toppo for teaching NSAID "delivered precisely to specific area of pain" (Examiner's Answer, p. 14). However, because the target headaches specified in the claims are *central* headaches, Toppo does not provide any evidence that a *topical* NSAID would work in treating a headache of *central* origin.

C) The Office has improperly combined Pradalier, Cluff, Toppo and Caldwell.

As explained in the Appellants' brief, the Examiner has failed to provide a sufficient valid reason to combine the references in the manner put forth by the Office.

In maintaining her position that the references have been properly combined, the Examiner has apparently based her reasoning to combine the references on the incorrect belief that NSAIDs 'block conduction' in target nerves. The Examiner has alleged that..."it would have been obvious to....deliver NSAID to keratinized skin proximal to target nerves...so the drug penetrates the skin to block conduction in the target nerves and provides pain relief...." (Examiner's Answer, pp. 5-6, emphasis added). In other words, the Examiner has alleged that the claimed "anti-inflammatory effective amount of a topical NSAID formulation" is blocking conduction in the target

nerves in order to provide the requisite reason to combine the references. This statement of the Examiner has no scientific or medical basis of support.

However, NSAIDs are non-steroidal anti-inflammatory agents which reduce inflammation. NSAIDS do not bind to sodium channels and do not block nerve condition.

As such, the Examiner's reasoning that one would combine the references because NSAIDS will block nerve conduction is not a valid reason because NSAIDs do not in fact block nerve conduction. Accordingly, the references have not been properly combined.

D. Conclusion

In sum, the above analysis demonstrates that the Examiner's prima facie case is insufficient because: not all of the elements of the claimed invention are present in the combined teaching of the references; the claimed invention represents an unexpected result; and the references have been improperly combined by the Office.

Group III: Claims 29-30

In maintaining the rejection of this group of claims, the Office has alleged that those of skill in the art would have optimized effective dosages and concurrent administration regimens as determined by good medical practice, and that such determination would have been routinely made, especially in view of the disclosure of Toppo that the topical doses of NSAIDs are greatly reduced more than the oral doses (Examiner's Answer, p. 22)

However, the claimed recited ranges in these claims are ranges that ensure topical delivery only, as opposed to ranges that would result in any systemic amounts of NSAID following topical application. As reviewed above, the combined teachings of the references fail to teach or suggest treating the recited target

headaches with anything but systemic levels of NSAIDs. As such, the specifically recited ranges of these method claims are not in fact taught or suggested by the cited combination of references.

As such, the Appellants' prior arguments still stand with equal force for the reasons discussed in the Appeal Brief and for the additional reasons discussed above.

In view of the foregoing discussion, the Applicants request that all remaining rejections be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

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